REMARKS

Claims 41-46, 48-50, 54-57 and 60-73 are pending in this application. Claims 41-46, 48-50, 54-57 and 60-73 were variously rejected under 35 U.S.C. §112, first paragraph. Claims 41-46, 48-50, 54-57 and 60-73 were rejected under 35 U.S.C. §112, second paragraph. Claims 41-46, 48, 49, 54, 55, 60, 61, 64, 65 and 68-71 were rejected under 35 U.S.C. §103.

By this amendment, claims 43, 54, 55, 60, 61, 64 and 67 have been canceled, claims 45, 46, 48, 56, 62, 65, 70, 71 and 72 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification. Support for the amendment to claim 65 is found, *inter alia*, at page 4, lines 28-31, page 7, lines 5-14, and page 21, line 10, through page 28, line 8.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

Applicants note with appreciation the Examiner's acknowledgement that claims 50, 56, 57, 62, 63, 66, 67, 72 and 73 appear to be free of the prior art of record.

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Written Description

Claims 54, 60, 61, 64, 66 and 67 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this ground for rejection.

In order to facilitate disposition of the present case, Applicants have cancelled claims 54, 60, 61, 64 and 67 without prejudice or disclaimer, making this rejection moot as it pertains to those claims.

With regard to claim 66, the Examiner asserts that "the specification does not contemplate administering RPE that are allogeneic to the host." Office Action, page 3. Applicants respectfully disagree. The specification states that "[w]ith local immunosuppression by a RPE cell-derived immunosuppressant agent, such as Fas L, there would be no cellular immunological attack waged against the transplanted cell, including the RPE cells themselves." Page 7, lines 15-18, emphasis added. Also, originally filed claim 12 recites that the "transplantation is by allograft," and claim 12 depends ultimately from claims 1 or 2 which recite only the administration of RPE cells. Thus, Applicants submit that the specification as filed describes administration of RPE cells which are allogeneic to the host and conveys to one skilled in the art possession of the invention with regard to claim 66.

In view of the foregoing, Applicants respectfully submit that the written description requirement has been met.

Enablement

Claims 41-46, 48-50, 54-57 and 60-73 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

The specification in its entirety provides sufficient guidance to teach one of skill in the art how to make and use the invention for facilitating survival of an allograft as claimed. Applicants respectfully traverse the Examiner's assertion that insufficient guidance is provided.

The claimed invention is directed to a method for facilitating survival of an allogeneic graft of non-RPE cells in a mammal through administering RPE cells and a population of non-RPE cells to a site in a mammal, where the non-RPE cells are allogeneic to the mammal. The RPE cells secrete Fas L and are administered in an amount effective to create localized immunosuppression at the site thereby increasing survival time of the allogeneic graft of the population of non-RPE cells in the mammal.

As noted by the Examiner, the specification demonstrates that RPE cells secrete the known immunosuppressive agent Fas L and that the Fas L secreted by RPE cells induces apoptosis in activated thymocytes. See, for example, the Example section on pages 16-28. The specification describes sources of RPE cells and describes and demonstrates isolating and culturing RPE cells, for example, on pages 8 and 16-20. Examples of non-RPE cells that may be administered with the RPE cells are provided, for example, on pages 6-7. The specification describes administration of the cells of the invention (see, for example, pages 15-16) and indicates that administration of these cells is accomplished by conventional techniques. Examples of dosage ranges of RPE cells are provided, for example, on page 15. Examples of assessments of immune rejection such as "histologically, or by functional assessment of the cotransplanted cells or tissue" are described, for example, on page 15. Accordingly, one skilled in the art would be able to assess survival of the transplanted cells. Such disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

Thus, Applicants submit that the claimed invention is enabled by the specification.

As acknowledged by the Examiner, "the art at the time of filing taught administering non-RPE into mammals to produce therapeutic molecules." Office Action, page 4. In addition, Ye[1] (of record) indicates that transplantation of RPE cells into a mammal was also known in the art at the time of filing.

The Examiner asserts that "RPE were known to provide "immune privilege" (Ye of record, 1993 ... ." Office Action, page 4. Applicants respectfully disagree with this assertion and characterization of Ye. Contrary to teaching that RPE cells provide immune privilege, Ye states that the "successful allotransplantation [of RPE cells] raises the possibility that the subretinal space of the rabbit might enjoy some degree of immunologic privilege." Ye, abstract, last line. Thus, according to Ye, the site of administration, the subretinal space, allows for the survival of the allotransplanted RPE cells.

The Examiner also asserts that the art at the time of filing did not "teach how to obtain therapeutic levels of biological molecules produced by non-RPE protected within an immune privileged site." Office Action, page 5. Applicants respectfully disagree with this assertion. Transplantation of non-RPE cells within an immune privileged site where the non-RPE cells produced therapeutic levels of a biological molecule have been described, for example, in Selawry et al. (1993, *Cell Transplantation* 2:123-129; of record) and in U.S. Patent No. 5,725,854, submitted herewith. These references describe a method of treating a disease that results from a deficiency of a biological factor by administration of Sertoli cells together with cells that produce the biological factor. The administered Sertoli cells create an immunologically privileged site "which prevents immune rejection of the subsequently or co-administered cells that produce the biological factor." U.S. Patent No. 5,725,854, column 7, lines 36-40 . In particular, these references demonstrate transplantation of Sertoli cells together with allogeneic islet cells in the renal subcapsular space of diabetic rats that results in some of the animals

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[1] Ye et al. (1993) *Current Eye Research* 12:629-639 ("Ye").

becoming normoglycemic. See, for example, Example 3 of U.S. Patent No. 5,725,854 (columns 12-15).

Thus, contrary to the Examiner's assertion regarding the activity of non-RPE protected with in an immune privileged site, non-RPE cells, as described in the present invention, have been successfully transplanted together with cells that create an immune privileged site such that the transplanted cells avoid rejection and produce a therapeutic amount of a biologically active molecule in the host.

Applicants respectfully submit that the standard for determining an enabling disclosure is not limited to what is described in a particular example of the specification. M.P.E.P. § 2164.02 states, for example, that "[c]ompliance with the enablement requirement does not turn on whether an example is disclosed" and "because only an enabling disclosure is required, applicant need not describe all actual embodiments." In fact, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).*

The claimed invention is directed to the use of RPE cells to create local immunosuppression to allow increased survival of co-transplanted, non-RPE cells as compared to survival of the non-RPE cells transplanted without the RPE cells. Applicant submits that a *prima facie* case of non-enablement has not been established and that the specification provides sufficient guidance for one skilled in the art to make and use the invention as claimed.

Accordingly, the pending claims are in compliance with the enablement requirements.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 41-46, 48-50, 54-57 and 60-73 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Although Applicants believe that the claims were sufficiently definite when considered in view of the specification and the understanding of those of skill in the art, Applicants have attempted to respond to the concerns of the Examiner in order to enhance clarity and to facilitate disposition of the present case.

Applicants respectfully note that claim 44 does not contain the phrase "said non-RPE cell population" and claim 47 was not pending. Applicants assume that the Examiner's comments regarding claims 44 and 47 were intended for claims 45 and 48 and have amended claims 45 and 48 to address the stated concerns.

The amendment to claim 46 clarifies that the re-administration of RPE cells is to maintain the immune privileged site that was created according to claim 65 and, accordingly, sustains the survival of the allogeneic non-RPE cells.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. §103

Claims 41-46, 48, 49, 54, 55, 60, 61, 64, 65 and 68-71 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Cherksey (U.S. Patent 5,618,531). Applicants respectfully traverse this rejection.

Applicants have cancelled claims 43, 54, 55, 60, 61, 64 and 67 without prejudice or disclaimer, rendering this ground for rejection moot as it pertains to those claims.

With regard to all of the rejected claims, Applicants respectfully point out that the cited reference does not support a *prima facie* case of obviousness with regard to the claimed invention.

As Applicants noted in the Amendment filed March 21, 2002, the present invention is based on the discovery that retinal pigment epithelial (RPE) cells secrete an immunosuppressive cytokine, Fas L, and can thereby produce a localized immunosuppressive environment at the site of RPE cell implantation. The claimed invention is directed to a method for facilitating survival of an allogeneic graft of non-RPE cells in a mammal through administering RPE cells and a population of non-RPE cells to a site in a mammal, wherein the non-RPE cells are allogeneic to the mammal. In the method, the RPE cells secrete Fas L and are administered in an amount effective to create localized immunosuppression at the site thereby increasing survival time of the allogeneic graft of the population of non-RPE cells.

Cherksey teaches administration of matrix-attached neural or paraneural cells, including RPE cells, to the brain for the treatment of a neurological disease and also describes "co-culture of neural or paraneural cells with glial cells, their co-incubation with a support matrix, followed by implantation of the support matrix carrying both cell types" (column 9, lines 3-6). As noted in Cherksey (column 8, line 65 through column 9, line 2), transplantation of glial cells into the brain was known in the art. Thus, Cherksey describes implantation of a support matrix carrying cell types which are known to survive implantation into the brain.

However, as discussed in the Amendment filed March 21, 2002, Cherksey does not teach or suggest that cells can secrete Fas L to create localized immunosuppression, much less that RPE cells secrete Fas L. Cherksey provides no guidance for the selection of RPE cells for the purpose of the present invention. Applicants thus submit that there is no motivation, either in the art or in the reference itself, for one skilled in the art to modify Cherksey to arrive at the presently claimed invention, i.e., administering RPE cells and allogeneic non-RPE cells to a site in a mammal to facilitate survival of the allogeneic graft of the non-RPE cells in the mammal.

Accordingly, Cherksey does not support *prima facie* obviousness with regard to the claimed invention.

In response to this argument put forth in the Amendment filed March 21, 2002, the Examiner in the pending final Office Action states that "Applicants argument is not persuasive because the claims do not require the RPE cells secrete Fas L or creating "localized immunosuppression." " Final Office Action, page 9. Applicants note that, as amended herein, the claims recite that "the RPE cells secrete Fas L" and that "the RPE cells are administered in an amount effective to create localized immunosuppression" at the site of administration.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSIONS

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000500. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: September 30, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the following amendments without prejudice or disclaimer.

In the Claims:

Please cancel claims 43, 54, 55, 60, 61, 64 and 67 without prejudice or disclaimer.

Please amend claims 45, 46, 48, 56, 62, 65, 70, 71 and 72 as follows.

45. (Three Times Amended) The method of claim 65 wherein said [non-RPE cell] population of non-RPE cells is administered in a dose ranging from 10^3 to 10^7 cells.

46. (Three Times Amended) The method of claim 65, further comprising re-administering RPE cells to the site in an effective amount to maintain the localized immunosuppression at the site and thereby sustain survival of the allogeneic non-RPE cells.

48. (Three Times Amended) The method of claim 46 wherein the re-administered RPE cells [for re-administration] are attached to a matrix prior to re-administration.

56. (Twice Amended) [The] A pharmaceutical composition [of claim 54] comprising retinal pigment epithelial (RPE) cells, a non-RPE cell population, and a pharmaceutically acceptable carrier, wherein said non-RPE cell population comprises insulin-producing cells.

62. (Three Times Amended) [The] A compartmentalized kit [according to claim 61] adapted to receive a first container adapted to contain retinal pigment epithelial (RPE) cells and a second container adapted to contain a non-RPE cell population, wherein the non-RPE cell population comprises insulin-producing cells.

65. (Amended) A method for facilitating survival of an allogeneic graft of a population of non-RPE cells in a mammal, comprising:

administering retinal pigment epithelial (RPE) cells and a population of non-RPE cells to a site in a mammal, wherein the population of non-RPE cells is allogeneic to the mammal, wherein the RPE cells secrete Fas L and wherein the RPE cells are administered in an amount effective to create localized immunosuppression at the site thereby increasing survival time of the allogeneic graft of the population of non-RPE cells in the mammal.

70. (Amended) The composition of claim [54] 56 wherein said RPE cells are attached to a matrix.

71. (Amended) The composition of claim [54] 56 wherein cells of said population of non-RPE cells are attached to a matrix.

72. (Amended) [The] An article of manufacture [according to claim 64], comprising:

a packaging material;

retinal pigment epithelial (RPE) cells contained within said packaging material;

a non-RPE cell population contained within said packaging material, wherein the non-RPE cell population comprises insulin-producing cells; and

wherein said packaging material contains a label that indicates that said RPE cells can be used for facilitating survival of an allogeneic graft of the non-RPE cell population in a mammal.